

Phase Transfer Catalyzed Selective Reduction of Bifunctional Moieties

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ABSTRACT

Reduction of bifunctional moieties to the corresponding alcohol is useful and one of the most important transformation in synthetic organic chemistry. Chemoselective reduction of one functional group in the presence of other functional groups is one of important interconversion in organic synthesis. A variety of catalysts have been developed to achieve this transformation. The present work reports the chemoselective reduction of aldehyde in the presence of Ketones using Sodium borohydride (NaBH_4) in Phase transfer catalyst at room temperature.

Keywords: Chemoselective reduction, bifunctional moieties, Sodium borohydride, aldehyde, ketones, phase transfer catalyst.

INTRODUCTION

Organic chemistry is not restrained by the limits of nature; only man's investigation defines the limits of the structural varieties that can be created. Exploration of known reaction points to new directions and development of new methodology offers the opportunity of streamlining the synthetic design and transformation¹. Reduction provides an important method for functional group interconversion in organic synthesis. Organic synthesis is the principal way to produce chemical products of practical

applications such as pharmaceuticals, plant protection agents, photographic chemicals, dyes, monomers etc². A phase transfer catalyst in chemistry is a catalyst which facilitates the migration of a reactant in a heterogenous system from one phase into another phase where reaction can take place. Ionic reactants are often soluble in aqueous phase but insoluble in an organic phase unless the phase transfer catalyst is present or it is a technique for conducting reaction between two or more reagents in two or more phases, when reaction is inhibited because the reactant cannot easily come together. A phase transfer agent is added to

transfer one of the reagent to a location where it can conveniently & rapidly react with another reagent. It is also necessary that the transferred species be in a highly active state when transferred, otherwise large amount of PTC will be required³. The catalyst was often a quaternary ammonium salt (e.g., tetrabutyl ammonium, $[\text{C}_4\text{H}_9]_4\text{N}^+$), also called the "quat" and symbolized by Q^+ , the ion pair Q^+X^- (X^- being the anion to be reacted) was a much looser ion pair than say Na^+X^- (Fig1) This looseness of the ion pair was a third key reason for enhanced reactivity, which would ultimately lead to increased productivity (reduced cycle time) in commercial processes. At the end of the reaction, an anionic leaving group was usually generated. This anionic leaving group was conveniently brought to the aqueous (or solid) phase by the shuttling catalyst, thus facilitated the separation of the waste material from the product. This mechanism is called the "extraction mechanism" of phase-transfer catalysis⁴.

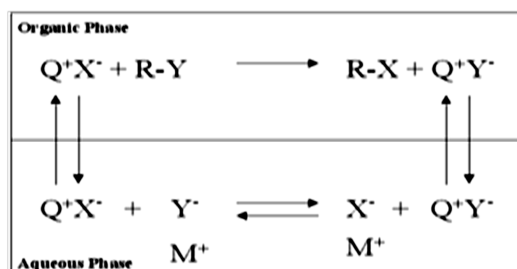


Fig. 1 Extraction mechanism

The transformation of starting material into desired final products usually required a number of chemical operations in which additional reagents, catalysts, solvents were used. The development of cleaner and safe synthetic methods and technologies for reduction to meet ever stricter environmental

regulations remain an active area of organic chemical research⁵. The stringent environment legislation had generated a pressing need for cleaner methods of chemical production, for instance, technologies that reduce or preferably, eliminate the generation of waste and avoid the use of toxic and hazardous reagents and solvents⁶. The green chemistry necessitated a paradigm shift from the traditional concept of process efficiency, that focuses exclusively on chemical yield, to one that assigns economic value to eliminating waste⁷.

RESULTS AND DISCUSSION

Reduction of aldehyde: The reduction of benzaldehyde was done under optimized conditions and completed in 5 sec (in 0.01molar ratio of TBAI & 0.4 molar ratio of NaBH_4 .) (Fig 2). Then the reduction of *p*-Chlorobenzaldehyde (Fig 3) was completed in same molar ratio. The progress of the reaction was followed by TLC. Then the reaction was completed within 30 sec. The reduction of *p*-Chlorobenzaldehyde, TLC taken after 5 sec (Fig 4) and after 30 sec (Fig 5) using mixture of solvents. (Ethyl acetate: Hexane, 1:9).

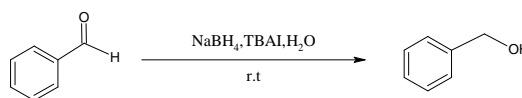


Fig. 2: Reduction of Benzaldehyde using NaBH_4 -TBAI

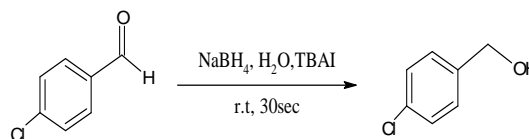


Fig 3: Reduction of *p*-Chlorobenzaldehyde using NaBH_4 -TBAI.

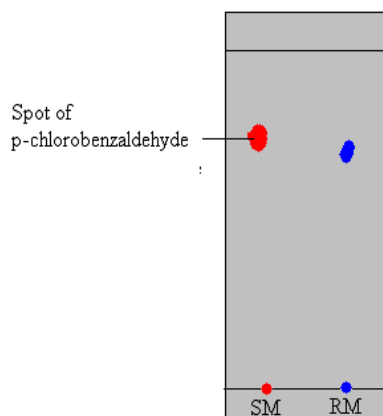


Fig 4 : Reduction of *p*-Chlorobenzaldehyde. TLC taken after 5 sec using mixture of solvents (EtoAc: Hexane, 1:9)

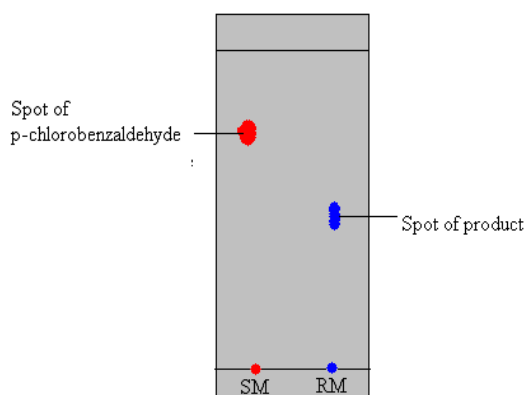


Fig 5: Reduction of *p* Chlorobenzaldehyde. TLC taken after 30 sec using mixture of solvents (EtoAc: Hexane, 1: 9)

Chemoselective reduction

In order to optimize the reaction condition, *p*-Chlorobenzaldehyde and acetophenone were selected as model compounds in H₂O as solvent at room temperature with different molar ratio of TBAI and NaBH₄. Equimolar mixture of *p*-Chlorobenzaldehyde (7 mmol) and

acetophenone (7 mmol) are subjected to react with NaBH₄- TBAI at room temperature (Fig 6), it was observed that the reduction of *p*-Chlorobenzaldehyde. The reaction mixture was monitored with TLC, which shows that *p*-Chlorobenzaldehyde was reduced and the reaction was complete within 30 sec under optimized reaction conditions (in 0.01 molar ratio of TBAI and 0.4 molar ratio of NaBH₄). The Chemoselective reduction of *p*-Chlorobenzaldehyde in the presence of acetophenone, TLC taken after 5 sec (Fig 7) and TLC taken after 30 sec (Fig 8).

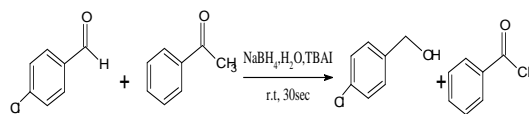


Fig. 6: Chemoselective reduction of *p*-Chlorobenzaldehyde in the presence of acetophenone.

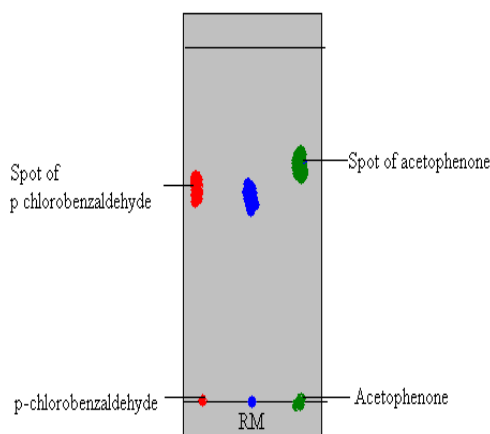


Fig 7: Chemoselective reduction of *p*-Chlorobenzaldehyde in the presence of acetophenone. TLC taken after 5 sec using mixture of solvents (EtoAc: Hexane, 1: 9)

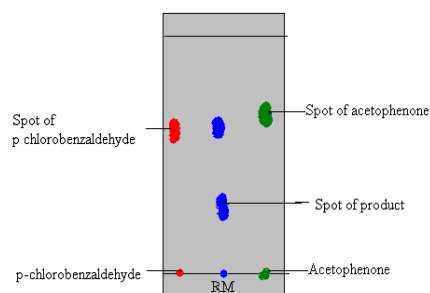


Fig 8: Chemoselective reduction of *p*-Chlorobenzaldehyde in the presence of acetophenone. TLC taken after 30 sec using mixture of solvents (EtoAc: Hexane, 1: 9)

The work up of the reaction was carried out and crude product was extracted with Ethyl acetate (EtoAc). Product was purified by using column chromatography, then characterized with IR. The IR spectra of the product shows absorption at 3416.05 cm^{-1} and devoid of absorption near $1725\text{--}1700\text{ cm}^{-1}$ has revealed the presence of --OH group and absence of --CHO moiety respectively and formation of Benzyl alcohol.

**Chemoselective Reduction of Aldehydes in the presence of Ketones
with NaBH_4 in TBAI at room temperature.**

Entry	Reactants	Product	Molar Ratio	Time
1			1:0.4:0.01	5min
2			1: 0.5: 0.01	5min
3			1: 0.6: 0.01	10 min
4			1: 0.4: 0.01	30 sec
5			1: 1: 0.4: 0.01	30 sec
6			1: 1: 0.4: 0.01	30 sec
7			1: 1: 0.4: 0.01	30 sec
8			1: 1: 0.4: 0.01	30 sec
9			1: 1: 0.4: 0.01	30 sec

To explore the synthetic utilities of these optimized conditions, we further examined with a pair of aldehyde with different ketones (Table 1).

Reducing agent – NaBH₄
PTC – TBAI
Solvent – H₂O
Temperature- rt

The products were characterized by comparison (TLC, IR) with authentic samples.

Table 1: Entry 5 FT-IR (cm⁻¹): 3416.05 cm⁻¹(-OH), 3018.7(C-H stretch), 1454.38 (Aromatic ring), 669.32 (parasbus). Table 4-1; **Entry 6** FT-IR (cm⁻¹): 3373.61cm⁻¹(-OH), 2524.9(C-H stretch), 144.73(Aromatic ring), 491.86(parasbus). Table 4-1; **Entry 7** FT-IR (cm⁻¹): 3416.05cm⁻¹(-OH), 3018.7(C-H stretch), 1491.02 (Aromatic ring), 702.11 (parasbus).

MATERIALS AND METHODS

All the solvents were dried and reactions were monitored by thin layer chromatography (TLC) using silica gel G. The products were characterized by a comparison with authentic samples. TLC was applied for the purity determination of substrates and products. Characterisation of the compound was done with Infrared Spectroscopy (IR). IR spectra were obtained from Instrumentation Laboratory (IL), Department Of Chemistry, Lovely Professional University, Phagwara on Shimadzu FT-IR 8400 spectrophotometer with maxima in cm⁻¹.

The mixture of compounds obtained during various reactions were purified over

silica gel by column chromatography. In all cases the column was packed in hexane and eluted with hexane followed by increasing percentage of ethylacetate. Various fractions were collected and distilled for the recovery of desired material. The last traces of the solvent were removed under suction. The products obtained were identified and compared over silica gel- G coated TLC plates. Plates were prepared by spreading as uniform thin layer of silica gel-G in the form of aqueous slurry, drying at room temperature and in oven for activation. The spotting of compounds were done by fine capillary and the plates were developed in hexane, ethyl acetate solvent varying proportions. Visualisation of spots were done by iodine chamber and by spraying 1ml H₂SO₄ – 9ml MeOH with a pinch of vanillin followed by heating at 120°C for 5 min.

General procedure for the Chemoselective reduction reaction(Scheme I)

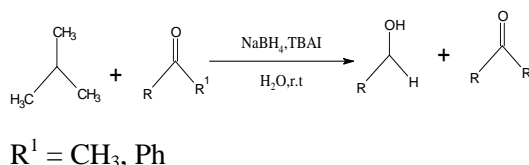


Fig 9: Chemoselective reduction of carbonyl groups.

In a two necked round-bottomed flask add Aldehyde and ketone/amide (1:1) and TBAI (.07 mmol). Then NaBH₄ (2 mmol) was dissolved in minimum quantity of water and then this solution was added dropwise to round bottom flask with constant stirring. The reaction was monitored using TLC. The reaction was completed in 30sec and then done the

extraction with chloroform. The crude products were purified by column chromatography on silica gel using a mixture of solvent (EtOAc: hexane) to get corresponding pure alcohols. Product was characterized with IR.

CONCLUSION

This technique demonstrated that the eco-friendly methods for the reduction of carbonyl compounds using NaBH_4 in the presence of TBAI. Chemoselective reduction of aldehyde in the presence of ketone, and amide was successfully achieved. Water, apart from being a green solvent and effectively controls the rate of the reaction. The present method offers an economical, safe, and environmentally benign procedure for the Chemoselective reduction of aldehydes in the presence of the other carbonyl compounds.

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